THE EFFECT OF ACETYLCHOLINE INFUSION ON THE PULMONARY CIRCULATION OF THE DOG AS REFLECTED BY CHANGES IN THE ARTERIAL OXYGEN TENSION

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CONTENTS

INTRODUCTION

After more than twenty-five years of research, the presence and significance of vasomotor activity in the pulmonary vascular bed remains a controversial subject of investigation. The difficulty arises in large part from the inability to provide an intact yet well controlled preparation in which such activity can be validly demonstrated. Daly (1) has recently emphasized the complexity of such a study. Active control of the pulmonary circulation by whatever stimulation, nervous, humoral, or gaseous, is demonstrated only under those conditions which wholly eliminate the participation of passive effects, namely cardiomotor, respiratory, bronchomotor, and bronchovascular.

Changes in cardiac output can be controlled by perfusing the lungs at a constant flow rate and pressure head, but while this preparation is adequate to demonstrate the effects of gaseous and drug stimulation, neural mechanisms require perfusion of the bronchial vascular system as well, in order to maintain the vitality of the nerve tissue (2). Such a procedure presents additional variables of bronchial artery pressure and bronchial vasomotor activity, since the bronchial vascular and pulmonary vascular systems are in communication (3,4).

Passive respiratory effects can be controlled by perfusion of the isolated lung or, in the intact animal, by controlling lung ventilation. Even with the precaution of a constant volume respiratory pump, however, gases inhaled or drugs infused may exert passive effects by bronchomotion. Thus, bronchoconstrictive agents, such as acetylcholine, will cause an increase in pulmonary vascular resistance due to a direct compression effect on the small vessels of the lung (5). This "false", or non-vascular, rise in pulmonary vascular resistance may play a role in thepresent study.

Neural stimulation of vasomotion has been adequately demonstrated in the perfused lung preparation. Stimulation of the thoraco-sympathetic nerves may result in intense vasoconstriction in the pulmonary circulation with pulmonary arterial pressure rises of up to 40 per cent of the resting value, whereas stimulation of the vagal vasodilator nerves has a much weaker effect (1,2). The dilator fiber effect is fully mimicked by acetylcholine in physiologic dosages (7). The role of the autonomic nervous system in the regulation of the pulmonary vascular bed has been reviewed by Halmagyi (8).

Although early experimenters had noted that the inhalation of carbon dioxide increased pulmonary vascular tone, as evidenced by a rise in pulmonary arterial pressure, von Euler and Liljestrand (9) were primarily responsible for the interest generated in the gaseous effects on the pulmonary

circulation. In cats they caused a rapid rise in pulmonary arterial pressure by reducing the oxygen tension of the inspired air to one-half its normal value. Conversely, they lowered the pulmonary arterial pressure by administering high concentrations of oxygen. Further, an increase in the carbon dioxide content of the inspired air was followed by a similar elevation of pulmonary arterial pressure of lesser magnitude. They concluded that the local pulmonary vascular bed was responsive to changing tensions of oxygen and carbon dioxide, and that the character of the response was to shunt blood away from underventilated or carbon dioxide contaminated alveoli. As the rise in pulmonary arterial pressure was not accompanied by a rise in left atrial pressure, it was assumed that pulmonary vascular resistance had been increased by hypoxia. Measuring the pulmonary arterial pressure, left atrial pressure, and cardiac output, Stroud and Rahn (10) subjected animals to stepwise reductions in the oxygen percentage of inspired air, and found resistance to increase in a graded fashion with increasing degrees of hypoxia. These findings have been shown to be true in man as well by Westcott el al (13) and other investigators (11, 12,14,15). The converse, that an enrichment of the oxygen content of alveolar air causes a reduction of pulmonary vascular resistance is somewhat less clear. Westcott et al (13) found no change in normal subjects ventilated with 100 per cent oxygen, but showed a significant decrease in

pulmonary arterial pressure in patients with pulmonary hypertension under the same conditions. More recently, similar findings have been reported in patients with mitral stenosis (16), congenital heart disease with pulmonary hypertension (17,18,19), and idiopathic pulmonary hypertension (20,21), although Marshall et al (22) found there to be no essential difference in the pulmonary vascular resistance under conditions of room air and 100 per cent oxygen ventilation in this latter group.

While the mechanism is not entirely clear, it is well established that hypoxic states are accompanied by vasoconstriction in the pulmonary bed, most pronounced when the resting pulmonary arterial pressure is elevated, and that hyperoxic states are accompaned by vasodilatation of lesser degree. The significance of these changes in the normal pulmonary circulation is undetermined. In an excellent review of the problem, Fishman (23) concludes that passive cardiorespiratory influences predominate over vasomotion in the regulation of the normal pulmonary circulation, and that respiratory gases act only as a fine adjustment of this circulation.

In general, drugs injected directly into the lesser circulation will act first on the pulmonary vascular bed, then on the more peripheral portions of the airway, and finally, by recirculation on the drug, on the bronchial and systemic circulations. The systemic pharmacologic effects

of acetylcholine are well known, and only a few points pertinent to the present study deserve reiteration here. In animals acetylcholine produces a generalized vasodilatation, especially of the smaller blood vessels, and a consequent fall in blood pressure. There is most often a bradycardia. The evanescent character of the response is due to two mechanisms: firstly, the rapid hydrolytic destruction of the ester by serum cholinesterase, and secondly, the opposition of the nicotinic effects of the drug, that is, the rise in arterial blood pressure and the cardioacceleration due to sympathoadrenal discharge mediated by the drug.

In man nearly all these effects are diminished, and although some vasodilatation occurs in the normal individual, the fall in blood pressure is minimal because of the rapid destruction mentioned above and the efficient compensatory cardiovascular reflexes mediated through the carotid pressoreceptors (24). The adrenal response may also play a role. Only in large doses (20-60 mg/min) are the systemic effects similar to those observed in animals. The bradycardia does not occur; in fact, cardioacceleration is more common. Systolic and diastolic blood pressure are not lowered appreciably, and there is no significant alteration in cardiac output.

in animals effective doses of acetylcholine may cause bronchospasm and hyperpnea is common, whereas in man there may be transient inspiratory difficulty, but in general the

respiratory effects are minimal even after large doses.

Thes species differences in the circulatory and respiratory response to acetylcholine may well account in part for the difficulty experienced in obtaining consistent results in animal experimentation. The relative insensitivity of the human systemic circulation and respiration to the effects of the drug may, with the aid of direct pulmonary artery infusion, so mitigate the systemic and passive respiratory effects as to allow for a clear demonstration of the pulmonary circulatory effect.

In general, animal experimentation with the drug has been disappointing, as both pulmonary vasoconstriction and vasodilatation have been reported (2,5,25,26). However, a certain trend was apparent in the early work with the drug in that low dosages were usually associated with pulmonary vasodilatation, evidenced by a fall in pulmonary arterial pressure, and higher dosages with vasoconstriction and a rise in pressure (7). Recently, Borst et al (27) infused acetylcholine into the pulmonary artery of one lung and, measuring the redistribution of blood flow as evidence of vasoactivity, demonstrated vasoconstriction in two dogs, vasodilatation in two, no change in one, and a diphasic response in another. Similarly Niden et al (28) found the response of the pulmonary arterial pressure following acetylcholine infusion to be inconsistent in the normal dog.

We are indebted to Harris (29) for the technique

presently used in assessing the effect of acetylcholine on the pulmonary circulation in man. Recognizing the fact that acetylcholine is rapidly destroyed in the bloodstream (6) and using the standard technique of right heart catheterization, Harris was able to infuse acetylcholine directly into the pulmonary artery in amounts small enough to insure its destruction before reaching the systemic circulation. The procedure required, however, accounts for the limited number of studies on the normal pulmonary circulation.

Fritts et al (11) were able to demonstrate a small but consistent fall in the pulmonary arterial pressure following acetylcholine infusion into 13 normal subjects, but the most productive studies have been those conducted in patients with a variety of cardiac and pulmonary diseases, whose common factor was an elevated resting pulmonary arterial pressure. Harris (30) was able to produce a fall in pulmonary arterial pressure in 18 of 47 patients, and noted that the magnitude of the response was directly related to the elevation of the resting pressure over a wide range, although patients with severe pulmonary hypertension were less responsive. He postulated that the vasodilatation produced by acetylcholine represented the release of a protective active vasoconstriction in the pulmonary vascular bed of these patients associated with medial muscular hypertrophy; and that with time and severity, fibrosis and permanent anatomical change was superimposed on this process,

making the vessels unresponsive to acetylcholine release. Wood et al (31) found a consistent decrease in pulmonary arterial pressure and calculated pulmonary vascular resistance following acetylcholine in patients with mitral stenosis and primary pulmonary hypertension. Wood (32) further suggested that the vasoconstriction in these patients may be secondary to the elevated pulmonary arterial pressure initially, but leads to further increases in the pressure, thus completing a vicious circle and resulting eventually in obliterative pulmonary hypertension. Soderholm and Werko (33) and others (34,35,36,37,38,39) have confirmed these findings in cases of mitral valvular disease. Similar changes in pulmonary arterial pressure and pulmonary vascular resistance have followed acetylcholine infusion in congenital heart disease with hypertension (18,19), primary pulmonary hypertension (21,22,32,43), and primary lung diseases (40,41,42). Left atrial pressure, heart rate, and cardiac output were measured in the majority of the above studies and found to be unchanged or insignificantly altered. Oakley et al (15) reported a decrease in pulmonary distending pressure and an increase in pulmonary blood volume with acetylcholine infusion, and concluded from these that active vasodilatation had been effected by the drug in patients with mitral disease.

The above studies clearly define the role of vasomotor tone in maintaining the pulmonary arterial pressure and pul-

monary vascular resistance in the disease states studied. However, the evidence for vasodilatation following acetylcholine in the normal man and dog is less convincing, and vasomotor activity appears to be of little physiologic significance in the normal pulmonary circulation.

Most recently, investigations have centered around the effect of acetylcholine on gas exchange in the lung, particularly the systemic arterial oxygen saturation (SaO_2). There was no significant change in SaO_2 accompanying the small pulmonary arterial pressure fall in normal human subjects, but when the vascular bed had been constricted by respiring a hypoxic mixture, acetylcholine produced a significant fall in SaO_2 (11). Soderholm and Werko (33) demonstrated a mean SaO_2 decrease of 7 per cent following acetylcholine in patients with mitral valvular disease, and these results have been confirmed by others (16,34,37,38), although this was not apparent in a study by Bishop et al (35). Similar findings have been reported in congenital heart disease (19) and pulmonary disease (40,41,42).

The mechanism of acetylcholine induced desaturation is unclear. The fact that it appears when the systemic effects of bronchoconstriction have been eliminated and in the presence of a normal or decreased arterial carbon dioxide tension makes it unlikely that there is alveolar hypoventilation secondary to a generalized bronchoconstrictor effect of the drug. Arteriovenous anastomoses have been

repeatedly demonstrated in the lung by Prinzmetal et al (44) and others (45,46,47,48,49), and the possibility exists that these are selectively dilated by acetylcholine, allowing venous blood to bypass the alveoli. Using the microsphere technique, Ring et al (51) has submitted evidence in favor of vasodilatation of these shunts with acetylcholine, although Rondell et al (50) had previously reported no effect with the drug. Stanfield et al (34) reported a lowering of the systemic arterial oxygen saturation and arterial oxygen tension (pO_2) with acetylcholine infusion in patients with mitral stenosis, but were able to eliminate both effects by allowing the patients to breathe 100 per cent oxygen. On this basis they concluded that no significant arteriovenous shunting had taken place and that the most probable mechanism of the desaturation was an alteration in the ventilation/perfusion ratio of the lung. If in certain areas of the lung alveolar hypoventilation exists, it will be attended by vasoconstriction due to the hypoxic stimulus, and therefore a low perfusion. The net result is a compensated non-uniform ventilation/perfusion ratio and normal arterial oxygen saturation and tension levels (52). With acetylcholine infusion vasodilatation occurs and the non-uniform ventilation/perfusion ratio is revealed, with a consequent fall in SaO_2 and pO_2.

Infusing acetylcholine into the pulmonary circulation of intact and perfused dog preparations, Niden et al (28)

were able to demonstrate a consistent fall in SaO_2 (average fall = 1.3 per cent) with the animals breathing room air. However, increasing the oxygen content of the inspired air to 30 per cent resulted in a diminution of the response, and with 100 per cent oxygen the effect was totally abolished. They concluded that while local ventilation/perfusion changes might well be responsible for the desaturation effect, true anatomical shunting could not be ruled out on the basis of the absence of the effect in the presence of 100 per cent oxygen. The degree of desaturation noted while breathing air was such that an anatomical shunt, if present, might have been masked by the administration of 100 per cent oxygen. This might result from the amount of oxygen dissolved in the plasma at this high arterial blood tension. Therefore, an anatomical shunt is not excluded by the elimination of the response with 100 per cent oxygen. In addition, the oximeter method used offers only limited accuracy in assessing small changes in oxygen saturation.

In view of the above, the present study was designed to avoid the relative insensitivity of the oxygen dissociation curve to changes at high oxygen levels by direct arterial oxygen tension measurements. In this way it was proposed to study the effect of acetylcholine infusion on the arterial oxygen tension under conditions of room air and 100 per cent oxygen ventilation.

MATERIALS AND METHODS

Seven mongrel dogs varying in weight from 6.4 to 15.4 kg were anesthetized with i.v. pentobarbital sodium (30 mg/kg). The trachea was cannulated and respiration controlled by means of a constant volume respiration pump (Model 667, Harvard Apparatus Co.) at a stroke volume of 150-300 cc and a rate of 16-22 strokes/min depending on the size and weight of the animal. A cylinder containing 100 per cent oxygen was attached to the pump via a balloon for those trials requiring ventilation with 100 per cent oxygen. In these cases the animal was allowed to inspire oxygen for at least five minutes before drug infusions were begun.

The electrocardiogram was monitored from Lead II throughout the experiments.

A Cournand catheter (No.6) was passed into the main pulmonary artery via the right external jugular vein and right heart, and was connected to a Statham pressure transducer (Model P23D) for the continuous measurement of pulmonary arterial pressure. This was recorded on a Gilson M8P recorder.

A second Cournand catheter (No.6) for the purpose of drug infusion was passed into the main pulmonary artery via the right femoral vein and situated just distal to the

pulmonic valve to insure the maximum drug effect on both lungs. The positions of the catheters were verified by pressure tracings and by fluoroscopy. Patency of the catheters was insured by intermittent flushing with 5% dextrose in water solution, to which 5mg/l heparin had been added. The infusion catheter was connected to a constant infusion/withdrawal pump (Model 600-900, Harvard Apparatus Co.), which provided for alteration in amount of drug and rate infused.

The right femoral artery was cannulated with polyethylene tubing (Intramedic, PE-240/S12) and connected via a second Statham pressure transducer to the Gilson recorder for continuous measurement of systemic arterial pressure.

The animal was anticoagulated with heparin solution (3 mg/kg).

Arterial oxygen tension was measured directly by means of a Severinghaus oxygen tension electrode and a Beckman Physiological Gas Analyzer (Model 160). The zero setting was established by flushing the electrode with nitrogen gas and the sensitivity span set to 150 mmHg with room air. The temperature of the electrode was maintained at 37°C by means of a water bath apparatus. Under these conditions the accuracy of the electrode was within 1 mmHg at room air and within 10 mmHg with 100 per cent oxygen.

The left femoral artery and vein were cannulated with polyethylene tubing (as above) and connected so as to

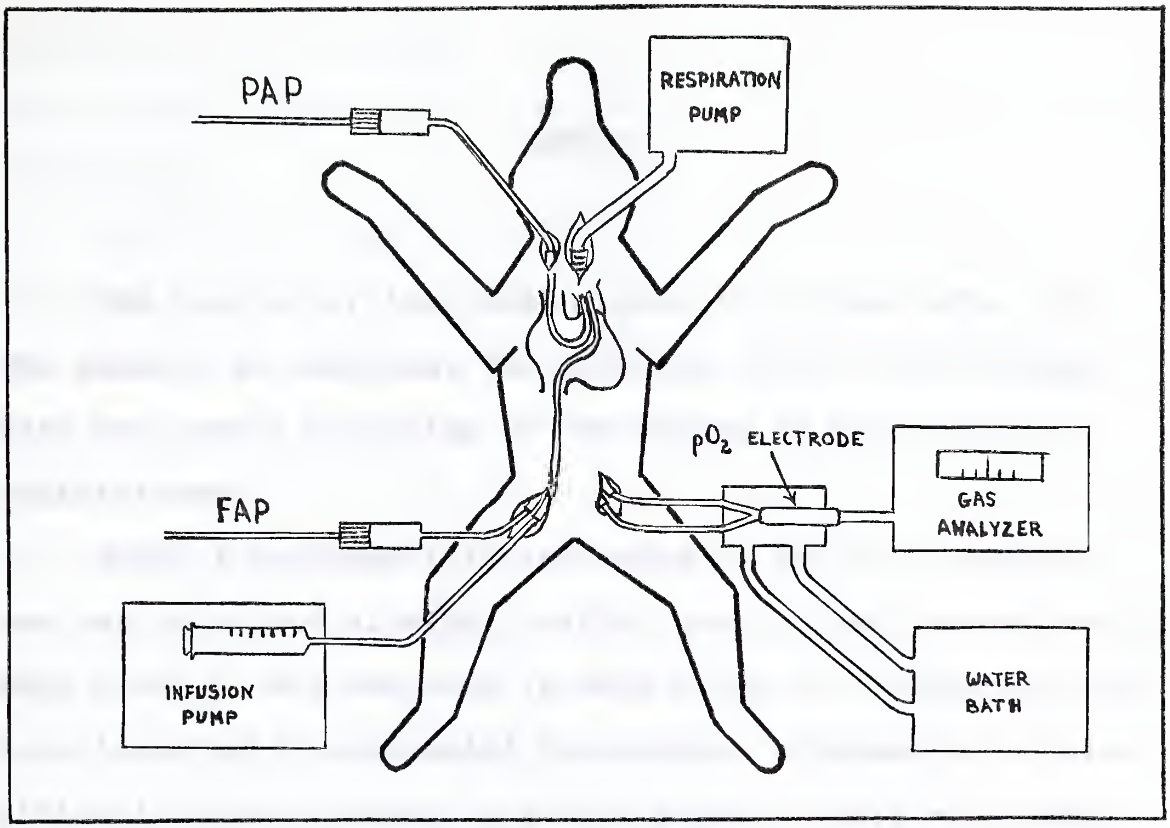
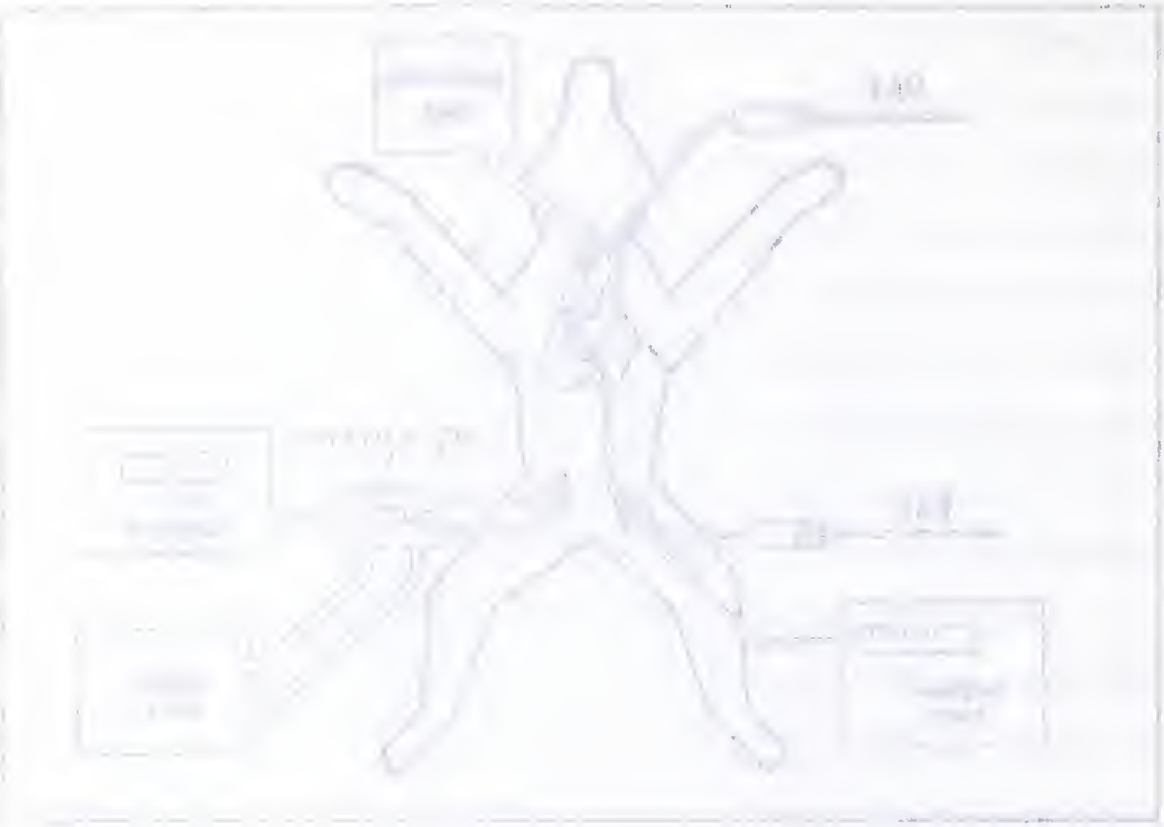


fig.1

provide a continuous flow of arterial blood past the electrode (fig.1). The rapidity of the response varied according to the membrane used but generally approximated five seconds.

Acetylcholine was freshly prepared and diluted just before use. Infusions were begun only after a suitable period of stabilized arterial oxygen tension recordings. Dosages varied from 0.005 to 2.0 mg/min and the amount infused never exceeded 5 cc. Infusions were continued until stable values were obtained for arterial oxygen tension, pulmonary arterial pressure, and systemic arterial pressure. This was usually apparent after two minutes of infusion.



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RESULTS

The results of the study appear in Tables I-IV. For the purpose of analysis, the infusion trials were divided into two groups according to the dosage of acetylcholine administered.

Group A included infusion rates of 1.0 to 2.0 mg/min and was comprised of eight trials, six of them carried out in Dogs 1 and 2, and one each in Dogs 3 and 5. Infusions here were invariably accompanied by systemic hypotension of significant degree (average systolic pressure fall = 84 mmHg; average diastolic fall = 63 mmHg). A significant bradycardia (average rate decrease = 28/min) was present in four trials, a slight tachycardia in three, and a marked tachycardia in one. Pulmonary arterial pressure changes were inconsistent in direction and generally of low magnitude (1-2 mmHg). The pulmonary arterial pressure rose in five trials, fell in one, and showed no essential change in two.

Respiring the animals with 100 per cent oxygen resulted in no apparent alteration of the acetylcholine effect when these trials were compared with those at room air in the individual dog or in the group. During the four trials with the animals breathing room air, the arterial oxygen tension fell consistently, although the magnitude of the fall varied

considerably (1-25 mmHg). Following ventilation with 100 per cent oxygen, however, the response was inconsistent and less significant.

Group B included a total of 21 infusion trials, nine of which were carried out with 100 per cent oxygen ventilation. The experiments involved Dogs 3,4,5,6, and 7. The dosage of acetylcholine infused varied from 0.005 to 0.5 mg/min. Systemic hypotension was similarly present in all trials, but was of lesser magnitude than in Group A (average systolic pressure fall = 20 mmHg; average diastolic fall = 19 mmHg). Acetylcholine infusion was accompanied by an increase in the heart rate in 15 of the 21 trials, by a slowing in three, and by no change in one. The pulmonary arterial pressure response showed some degree of specificity in the individual animals. Dog 3 responded to the infusions with an increase in pulmonary arterial pressure in all trials, and with a further increase (8 mmHg) upon ventilation with 100 per cent oxygen. Dogs 4,5,6, and 7 showed both elevation and depression of the pulmonary arterial pressure. These changes bore no apparent relationship in direction or degree to the oxygen content of the inspired gas.

The arterial oxygen tension effects were slight and inconsistent. While respiring room air, Dog 3 showed both a rise and a fall in pO_2. In the case of Dog 4, the lowering of arterial pO_2 was more prominent; in Dog 5 there was either a lowering or no change. However the pO_2 rose in Dog 6, and

both a rise and a fall were present in Dog 7. With 100 per cent oxygen ventilation, two animals (3 and 4) showed an elevation of arterial pO_2; three (5,6, and 7) responded with a fall in pO_2.

TABLE I

Effect of acetylcholine infusion in Group A

Dog	Rate mg/min	FiO_2	SAP S	SAP D	PAP S	PAP D	pO_2 mmHg	Heart rate
1	2.0	1.00	170	110	4	2	600	128
(8.4 kg)			55	30	6	3	600	136
	2.0	.21	155	115	3	2	100	128
			60	35	5	2	-	132
	2.0	.21	125	70	13	4	105	204
			45	25	6	2	80	164
	2.0	1.00	70	40	5	2	600	176
			40	25	4	3	580	160
2	2.0	.21	205	137	31	4	97	220
(12.5 kg)			67	37	30	8	96	184
	2.0	1.00	200	155	10	3	610	148
			100	72	27	5	620	216
3	1.0	.21	115	85	13	7	92	180
(12.5 kg)			55	35	17	7	78	160
5	1.0	.21	93	62	17	10	90	132
(6.4 kg)			25	10	18	11	86	140

FiO_2 = Fraction of oxygen in the inspired air
SAP = Systemic arterial pressure
PAP = Pulmonary arterial pressure
S = Systolic
D = Diastolic
pO_2 = systemic arterial oxygen tension

TABLE II

Summary of changes in Group A

Dog	Rate mg/min	FiO_2	SAP S	SAP D	PAP S	PAP D	pO_2 mmHg	Heart rate
1	2.0	1.00	-115	-70	+2	+1	0	+8
	2.0	.21	-95	-80	+2	0	inc	+4
	2.0	.21	-80	-45	-7	-2	-25	-40
	2.0	1.00	-30	-15	-1	+1	-20	-16
2	2.0	.21	-138	-100	-1	+4	-1	-36
	2.0	1.00	-90	-82	+17	+2	+10	+64
3	1.0	.21	-60	-50	+4	0	-14	-20
4	1.0	.21	-68	-52	+1	+1	-4	+8

TABLE III

Effect of acetylcholine infusion in Group B

Dog	Rate mg/min	FiO_2	SAP		PAP		pO_2 mmHg	Heart rate
			S	D	S	D		
3	0.5	.21	103	80	10	6	78	168
(12.5 kg)			87	62	11	6	-	168
	0.5	1.00	115	87	8	5	500	176
			95	60	16	7	510	180
	0.5	.21	130	102	9	4	61	184
			110	72	13	6	65	180
4	0.1	.21	62	32	15	6	85	78
(9.4 kg)			40	20	12	6	86	76
	0.1	1.00	60	35	15	8	380	82
			35	18	14	7	-	88
	0.1	1.00	78	55	9	6	335	94
			52	27	10	7	395	100
	0.1	.21	100	73	7	4	90	110
			70	30	9	5	85	84
	0.05	.21	96	73	6	4	79	100
			95	70	6	4	75	104
5	0.5	.21	60	32	18	8	88	114
(6.4 kg)			57	30	20	10	84	118
	0.5	.21	90	60	21	10	87	118
			49	25	25	13	87	134
	0.5	1.00	110	80	25	11	565	126
			85	50	27	13	560	144
	0.5	1.00	122	85	27	11	565	132
			100	57	30	14	565	156

TABLE III (cont.)

Dog	Rate mg/min	FiO_2	SAP		PAP		pO_2 mmHg	Heart rate
			S	D	S	D		
	0.5	1.00	130	88	28	12	575	132
			70	40	28	12	565	140
	0.25	1.00	117	82	27	11	565	120
			92	56	25	11	560	130
	0.25	.21	78	42	28	12	94	128
			70	40	23	12	94	124
	0.25	.21	90	57	24	11	93	128
			80	49	23	12	91	128
6	0.01	.21	185	130	26	12	146	196
(13.2 kg)			180	135	28	15	152	196
	0.005	1.00	200	145	26	13	675	176
			190	135	24	12	665	188
	0.01	.21	215	145	26	12	77	136
			190	140	27	12	81	176
7	0.01	.21	145	95	17	8	88	224
(15.4 kg)			130	80	14	8	91	248
	0.25	1.00	132	87	15	4	620	220
			112	82	16	4	600	244

TABLE IV

Summary of changes in Group B

Dog	Rate mg/min	FiO_2	SAP S	SAP D	PAP S	PAP D	pO_2 mmHg	Heart rate
3	0.5	.21	-16	-18	+1	0	inc	0
	0.5	1.00	-20	-27	+8	+2	+10	+4
	0.5	.21	-20	-30	+4	+2	+4	-4
4	0.1	.21	-22	-12	-3	0	+1	-2
	0.1	1.00	-25	-17	-1	-1	inc	+6
	0.1	1.00	-26	-28	+1	+1	+60	+6
	0.1	.21	-30	-43	+2	+1	-5	-26
	0.05	.21	-1	-3	0	0	-4	+4
5	0.5	.21	-3	-2	+2	+2	-4	+4
	0.5	.21	-41	-35	+4	+3	0	+16
	0.5	1.00	-25	-30	+2	+2	-5	+18
	0.5	1.00	-22	-28	+3	+3	0	+14
	0.5	1.00	-60	-48	0	0	-10	+8
	0.25	1.00	-25	-22	-2	0	-5	+10
	0.25	.21	-8	-2	-1	0	0	+4
	0.25	.21	-10	-8	-1	+1	-2	0
6	0.01	.21	-5	+5	+2	+3	+6	0
	0.005	1.00	-10	-10	-2	-1	-10	+12

TABLE IV (cont.)

Dog	Rate mg/min	FiO_2	SAP		PAP		pO_2 mmHg	Heart rate
			S	D	S	D		
	0.01	.21	-25	-5	+1	0	+4	+40
7	0.01	.21	-15	-15	-3	0	-20	+24
	0.25	1.00	-20	-15	+1	0	-20	+24

DISCUSSION

Systemic Arterial Pressure

The rapid and severe systemic hypotension which invariably followed infusion of larger doses of acetylcholine (Group A) is characteristic of and attributable to systemic vasodilatation as a direct effect of the drug (24). In all cases the pressure resumed its normal level when the infusion had been discontinued. Following smaller dosages of acetylcholine (Group B) this effect was still present, though less marked.

Heart Rate

The bradycardia following acetylcholine infusion in Group A is also attributable to a direct effect on the heart (the "vagal effect"). With smaller doses of the drug (Group B), however, the predominant response was cardioacceleration, which most likely represents reflex inhibition of vagal tone mediated via the aortic and carotid baroreceptors in response to the systemic hypotension. In the absence of sufficient drug to produce the slowing of the heart rate seen in Group A, this latter effect predominates, with the consequent tachycardia.

Pulmonary Arterial Pressure

In general, acetylcholine infusion in Group A was attended by a rise in pulmonary arterial pressure. Assuming that the decrease in systemic pressure and heart rate already mentioned are evidence of a generalized acetylcholine effect on the systemic circulation in this group, it is most probable that the characteristic respiratory effect, namely generalized bronchoconstriction, was also present. While the respiratory volume was maintained by a constant volume respiration pump, the intratracheal pressure was not measured and cannot be assumed to have remained constant. Bronchoconstriction might easily have accounted for the rise in pulmonary arterial pressure in this group in a passive manner, making it unnecessary to invoke a primary drug effect on the pulmonary circulation.

With smaller doses of acetylcholine (Group B) the pulmonary arterial pressure response was less consistent, with both increases and decreases being observed. As the effects of acetylcholine are dose related, bronchoconstriction, while present, plays a lesser role in this group. In addition, significant alterations in systemic pressure and heart rate can be expected to reduce cardiac output and cause a passive lowering of pulmonary arterial pressure in this way. In most trials the changes observed represent the net effect of these passive forces. When only those trials were considered, wherein changes in systemic pressure and

heart rate were insignificant, the pulmonary arterial pressure response was minute and inconsistent. These findings are in agreement with those of Borst et al (27) and Niden et al (28).

It is interesting that in four animals (Dogs 1,2,3, and 7) pulmonary arterial pressure fell upon ventilation with 100 per cent oxygen. In the absence of systemic effect, this may represent pulmonary vasodilatation similar to that observed by von Euler and Liljestrand in the cat (9).

Arterial Oxygen Tension

Changes in arterial oxygen tension may ordinarily result from any of the following: (a) changes in ventilation (volume or distribution), (b) changes in diffusion of oxygen from the alveolus to the blood, (c) changes in perfusion, overall or local, (d) opening or closing of arteriovenous anastomoses, or (e) artefacts in measurement.

The results of acetylcholine infusion in Group A show a consistent fall in arterial oxygen tension, but in view of the systemic drug effects in this group this finding is less significant. Generalized hypoventilation secondary to the bronchoconstriction already mentioned is probably the central factor in lowering the arterial oxygen tension in this series. With 100 per cent oxygen ventilation, arterial oxygen tension changes are minimal and inconsistent, which lends support to the role of this factor.

Arterial oxygen tension changes in Group B were of small magnitude and varied direction. As the systemic effects were less marked in this group, it is unlikely that changes in overall ventilation and perfusion contributed appreciably to these changes. While either local changes in ventilation/perfusion ratio or true anatomical shunting may be present, the inconsistency of the response makes these factors difficult to evaluate. In addition, artefacts of measurement due to delayed electrode response, stagnation of the shunted blood in the area of the electrode, and the normal margin of error of the electrode may well account for changes of this magnitude. Therefore, it may be concluded that within the limits of the above preparation, no significant alteration in the arterial oxygen tension could be demonstrated following acetylcholine infusion.

In the demonstration and assessment of acetylcholine induced vasodilatation the experimental approach is limited by (a) the participation of passive effects, as discussed earlier, and (b) the small magnitude of the response in the normal pulmonary vasculature. While it is theoretically possible to increase the sensitivity of the recording apparatus, one might better attack the latter problem by enhancing the pulmonary vascular response to the drug infused. Recognizing that the magnitude of the dilatation response is directly related to the resting tone of the vessels, Rudolph et al (53) increased the resting tone of

the pulmonary vasculature in dogs by infusing serotonin prior to acetylcholine trials. In this way they were able to demonstrate a consistent fall in the pulmonary arterial pressure following acetylcholine in the serotonin-constricted pulmonary vessels. While the use of a second drug imposes additional variables on the experimental system, this technique seems worthy of trial in studies designed to elucidate the effect of acetylcholine on the arterial oxygen tension.

SUMMARY

Acetylcholine in varying dosages was infused directly into the pulmonary artery of seven dogs, under conditions of room air and 100 per cent oxygen ventilation, and the changes in arterial oxygen tension recorded.

With larger dosages of the drug, effects on the pulmonary vasculature and changes in arterial oxygen tension were masked or obliterated by the predominating systemic effect of the drug.

With smaller dosages, changes in the arterial oxygen tension were apparent but were generally of small magnitude and inconsistent direction.

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